In the Specification:

Please amend the specification as shown:

Please delete the paragraph on page 27, line 26, through page 28, line 9, and replace it with the following paragraph:

a1

Additionally, specific groups of amino acids may be incorporated into the conjugate to facilitate metabolism by specific enzymes. Enzymes such as the metalloproteinases (e.g. cathepsin-D) are known to hydrolzye specific amino acid sequences. Metalloproteinases, for example, are overexpressed in certain body sites, e.g. in inflammation, angiogenesis and cancer. (Tung, C.H., et al., (1999) Bioconjugate Chem. 10:892-896). Thus, incorporating a cleavable peptide sequence into a conjugate may serve to improve delivery of bioactive agents to the desired tissue. As an example, the octapeptide GPICFRLG **(SEQ ID NO: 1)** or the variant GPIFFRLC **(SEQ ID NO: 2)** is a substrate for cathepsin-D. This peptide may be annealed to the C-terminus of a hydrophobic peptide, such as polyleucine, to generate a site for controlled cleavage. Similarly, endopeptidase sites such as -VLK-, which are sites for plasmin, may be utilized in the construct, for example, to mimic the action of plasmin cleaveage of fibringogen into fibrin during clot formation. Those of skill in the art will readily note that trypsin, chymotrypsin, papain and other endopeptidase-susceptible sites could also be annealed into the construct.

Please delete the paragraph on page 32, lines 14-15, and replace it with the following paragraph:

a2

Brain Homing Peptides: CNSRLHLRC **(SEQ ID NO: 3)**, CENWWGDVC **(SEQ ID NO: 4)**, WRCVLREGPAGGCAWFNRHRL **(SEQ ID NO: 5)**, and CLSSRLDAC **(SEQ ID NO: 6)**.

Please delete the paragraph on page 32, lines 16-18, and replace it with the following paragraph:

a3

Kidney Homing Peptides: CLPVASC **(SEQ ID NO: 7)**, and CGAREMC **(SEQ ID NO: 8)**. Cyclized disulfides of the foregoing brain and kidney homing peptides are particularly preferred.

Please delete the paragraph on page 32, lines 19-30, and replace it with the following paragraph:

a4

Peptides recognized by fibronectin- and vitronectin-binding integrins may also be useful as targeting agents in accordance with the present invention. These motifs include the amino acid sequences DGR, NGR, and CRGDC **(SEQ ID NO: 9)**. These peptides are generally characterized by their ability to inhibit integrin-expressing cells from binding to extracellular matrix proteins, and in particular the binding of fibronectin to 5- 1 integrin. Embodiments of these types of peptides include the linear or cyclic peptide motifs CRGDCL **(SEQ ID NO: 10)**, NGR(AHA) **(SEQ ID NO: 11)** and DGR(AHA) **(SEQ ID NO: 12)**. The CRGDCL **(SEQ ID NO: 10)** peptide has a high binding affinity, which may make it useful as a general inhibitor and mediator of RGD-dependent cell attachment. Another preferred targeting ligand is the peptide CRGDCA **(SEQ ID NO: 13)**. Both the NGR(AHA) **(SEQ ID NO: 11)** and DGR(AHA) **(SEQ ID NO: 12)** peptides contain the AHA sequence, which is not believed to be essential for binding, as indicated by the parentheses surrounding this sequence. The NGR sequence shows some selectivity toward the α-v-β5 integrin.

Please delete the paragraph on page 33, lines 1-4, and replace it with the following paragraph:

a5

Additional peptides which may be useful to bind α5-β1 integrin are those which include the peptide motifs RCDVVV **(SEQ ID NO: 14)**, SLIDIP **(SEQ ID NO: 15)**, and TIRSVD **(SEQ ID NO: 16)**. Peptides which may preferentially bind α5-β1 integrin include the following motifs: KRGD **(SEQ ID NO: 17)**, RRGD **(SEQ ID NO: 18)**, and RGDL **(SEQ ID NO:**

19).

Please delete the paragraph on page 33, lines 5-10, and replace it with the following paragraph:

a6

Peptide sequences which may also be useful as targeting ligands in the present compositions include those which may form -RGD- type binding determinants of antibodies and include the following: CSFGRGDIRNC **(SEQ ID NO: 20)**, CSFGRTDQRIC **(SEQ ID NO: 21)**, CSFGKGDNRIC **(SEQ ID NO: 22)**, CSFGRNDSRNC **(SEQ ID NO: 23)**, CSFGRVDDRNC **(SEQ ID NO: 24)**, CSFGRADRRNC **(SEQ ID NO: 25)**, CSFGRSVDRNC **(SEQ ID NO: 26)**, CSFGKRDMRNC **(SEQ ID NO: 27)**, CSFGRWDARNC **(SEQ ID NO: 28)**, CSFGRQDVRNC **(SEQ ID NO: 29)**, and CSFGRDDGRNC **(SEQ ID NO: 30)**.

Please delete the paragraph on page 33, lines 11-12, and replace it with the following paragraph:

a7

To target angiogenic endothelium of solid tumors, suitable targeting ligands include the following peptides: CDCRGDCFC **(SEQ ID NO: 31)** and CNGRCVSGCAGRC **(SEQ ID NO: 32)**.

Please delete the paragraph on page 33, lines 13-23, and replace it with the following paragraph:

a8

Other peptide sequences chosen for tissue specificity and which may be useful as targeting ligands in the present invention include the following:

Lung: CGFECVRQCPERC **(SEQ ID NO: 33)**, CGFELETC **(SEQ ID NO: 34)**, CTLRDRNC **(SEQ ID NO: 35)** and CIGEVEVC **(SEQ ID NO: 36)**

Skin: CVALCREACGEGC **(SEQ ID NO: 37)**

Pancreas: SWCEPGWCR **(SEQ ID NO: 38)**

Intestine: YSGKWGW **(SEQ ID NO: 39)**

a8 con't

Uterus: GLSGGRS (SEQ ID NO: 40)

Adrenal Gland: LMLPRAD (SEQ ID NO: 41)

Retina: CRDVVSVIC (SEQ ID NO: 42) and CSCFRDVCC (SEQ ID NO: 43)

See, e.g., Rajotte, et. al., (1998) J. Clin. Invest., 102:430-437, the disclosures of which are hereby incorporated herein by reference, in their entirety.

Please delete the paragraph on page 33, line 24, through page 41, line 3, and replace it with the following paragraph:

a9

Cationic peptides (SEQ ID NOS 44-120, respectively, in order of appearance), including, but not limited to those set out in Table 1 below, are also preferred for use as targeting ligands, particularly due to their specificity for various cancers:

TABLE 1

GROUP NAME	PEPTIDE	SEQUENCE	REFERENCE*
Abaecins	Abaecin	YVPLPNVPQPGRRPFPTFPG QGPFNPKIKWPQGY	Casteels et al. (1990)
Andropins	Andropin	VFIDILDKVENAIHNAAQVG IGFAKPFEKLINPK	Samakovlis et al.(1991)
Apidaecins	Apidaecin 1A	GNNRPVYIPQPRPPHPRI	Casteels et al. (1989)
	Apidaecin 1B	GNNRPVYIPQPRPPHPRL	Casteels et al. (1989)
	Apidaecin II	GNNRPIYIPQPRPPHPRL	Casteels et al. (1989)
AS	AS-48	7.4 kDa	Galvez et al. (1989)
Bactenecins	Bactenecin	RLCRIVVIRVCR	Romeo et al. (1988)
Bac	Bac5	RFRPPIRRPPIRPPFYPPFRPP IRPPIFPPIRPPFRPPLRFP	Frank et al. (1990)

a9 cont

GROUP NAME	PEPTIDE	SEQUENCE	REFERENCE*
	Bac7	RRIRPRPPRLPRPRPRPLPFP RPGPRPIPRPLPFPRPGPRPI PRPLPFFRPGPRPIPRP	Frank et al. (1990)
Bactericidins	Bactericidin B2	WNPFKELERAGQRVRDAVI SAAPAVATVGQAALARG*	Dickinson et al (1988)
	Bactericidin B3	WNPFKELERAGQRVRDAIIS AGPAVATVGQAAAIARG*	Dickinson et al (1988)
	Bactericidin B4	WNPFKELERAGQRVRDAIIS AAPAVATVGQAAAIARG*	Dickinson et al (1988)
	Bactericidin B-5P	WNPFKELERAGQRVRDAVI SAAPAVATVGQAAAIARG G*	Dickinson et al. (1988)
Bacteriocins	Bacteriocin C3603	4.8 kDa	Takada et al. (1984)
	Bacteriocin IY52	5 kDa	Nakamura et al. (1983)
Bombinins	Bombinin	GIGALSAKGALKGLAKGLA ZHFAN*	Csordas and Michi (1970)
	BLP-1	GIGASILSAGKSALKGLAKG LAEHFAN*	Gibson et al. (1991)
	BLP-2	GIGSAILSAGKSALKGLAKG LAEHFAN*	Gibson et al. (1991)
Bombolitins	Bombolitin BI	JIKITTMLAKLGKVLAHV*	Argiolas and Pisano (1985)
	Bombolitin BII	SKITDILAKLGKVLAHV*	Argiolas and Pisano (1985)
BPTI	Bovine Pancreatic Trypsin Inhibitor (BPTI)	RPDFCLEPPYTGPCKARIIRY FYNAKAGLCQTFVYGGCR AKRNNFKSAEDCMRTCGG A	Creighton and Charles (1987)

a9 cont

GROUP NAME	PEPTIDE	SEQUENCE	REFERENCE*
Brevinins	Brevinin-1E	FLPLLAGLAANFLPKIFCKIT RKC	Simmaco et al. (1993)
	Brevinin-2E	GIMDTLKNLAKTAGKGALQ SLLNKASCKLSGQC	Simmaco et al. (1993)
Cecropins	Cecropin A	KWKLFKKIEKVGQNIRDGIIK AGPAVAVVGQATQIAK*	Gudmundsson et al. (1991)
	Cecropin B	KWKVFKKIEKMGRNIRNGI VKAGPAIAVLGEAKAL*	Xanthopoulas et al. (1988)
	Cecropin C	GWLKKLGKRIERIGQHTRD ATIQGLGIAQQAANVAATA RG*	Tryselius et al. (1992)
	Cecropin D	WNPFKELEKVGQRVRDAVI SAGPAVATVAQATALAK*	Hultmark et al. (1982)
	Cecropin P	SWLSKTAKKLENSAKKRIS EGIAIAIQGGPR	Lee et al. (1989)
Charybdtoxins	Charybdtoxin	ZFTNVSCTTSKECWSVCQ RLHNTSRGKCMNKKCRCY S	Schweitz et al. (1989)
Coleoptericins	Coleoptericin	8.1 kDa	Bulet et al. (1991)
Crabolins	Crabolin	FLPLILRKIVTAL*	Argiolas and Pisano (1984)
α-Defensins	Cryptbin 1	LRDLVCYCRSRGCKGRERM NGTCRKGHLLYTLCCR	Selsted et al. (1992)
	Cryptbin 2	LRDLVCYCRTRGCKRRERM NGTCRKGHLMYTLCCR	Selsted et al. (1992)
	MCP1	VVCACRRALCLPRERRAGF CRIRGRIHPLCCRR	Selsted et al. (1983)
	MCP2	VVCACRRALCLPLERRAGF CRIRGRIHPLCCRR	Ganz et al. (1989)

a9 cont

GROUP NAME	PEPTIDE	SEQUENCE	REFERENCE*
	GNCP-1	RRCICTTRTCRFPYRRLGTCI FQNRVYTFCC	Yamashita and Saito (1989)
	GNCP-2	RRCICTTRTCRFPYRRLGTC LFQNRVYTFCC	Yamashita and Saito (1989)
	HNP-1	ACYCRIPACIAGERRYGTCI YQGRLWAFCC	Lehrer et al. (1991)
	HNP-2	CYCRIPACIAGERRYGTCIY QGRLWAFCC	Lehrer et al. (1991)
	NP-1	VVCACRRALCLPRERRAGF CRIRGRIHPLCCRR	Ganz et al. 1989
	NP-2	VVCACRRALCLPLERRAGF CRIRGRIHPLCCRR	Ganz et al. 1989
	RatNP-1	VTCYCRRTRCGFRERLSGA CGYRGRIYRLCCR	Eisenhauer et al. (1989)
	RatNP-2	VTCYCRSTRCGFRERLSGA CGYRGRIYRLCCR	Eisenhauer et al. (1989)
β-Defensins	BNBD-1	DFASCHTNGGICLPNRCPG HMIQIGICFRPRVKCCRSW	Selsted et al. (1993)
	BNBD-2	VRNHVTCRINRGFCVPIRCP GRTRQIGTCFGPRIKCCRS W	Selsted et al. (1993)
	TAP	NPVSCVRNKGICVPIRCPGS MKQIGTCVGRAVKCCRKK	Diamond et al. (1991)
Defensins-insect	Sapecin	ATCDLLSGTGINHSACAAH CLLRGNRGGYCNGKAVCV CRN	Hanzawa et al. (1990)
	Insect defensin	GFGCPLDQMQCHRHCQTI TGRSGGYCSGPLKLTCTCY R	Bulet et al. (1992)
Defensins-	Scorpion	GFGCPLNQGACHRHCRSIR	Cociancich et al.

GROUP NAME	PEPTIDE	SEQUENCE	REFERENCE*
scorpion	defensin	RRGGYCAGFFKQTCTCYRN	(1993)
Dermaseptins	Dermaseptin	ALWKTMLKKLGTMALHAGKAALGAADTISQTQ	Mor et al. (1991)
Diptericins	Diptericin	9 kDa	Reichhardt et al. (1989)
Drosocins	Drosocin	GKPRPYSPRPTSHPRPIRV	Bulet et al. (1993)
Esculentins	Esculentin	GIFSKLGRKKIKNLLISGLKNVGKEVGMDVVRTGIDIAGCKIKGEC	Simmaco et al. (1993)
Indolicidins	Indolicidn	ILPWKWPWWPWRR*	Selsted et al. (1992)
Lactoferricins	Lactoferricin B	FKCRRWQWRMKKLGAPSITCVRRAP	Bellamy et al. (1992b)
Lantibiotics	Nisin	ITSISLCTPGCKTGALMGCNMKTATCHCSIHVSK	Hurst (1981)
	Pep 5	TAGPAIRASVKQCQKTLKATRLFTVSCKGKNGCK	Keletta et al. (1989)
	Subtilin	MSKFDDFDLDVVKVSKQDSKITPQWKSESLCTPGCVTGALQTCFLQTLTCNCKISK	Banerjee and Hansen (1988)
Leukocons	Leukocin A-val 187	KYYGNGVHCTKSGCSVNWGEAFSAGVHRLANGGNGFW	Hastings et al. (1991)
Magainins	Magainin I	GIGKFLHSAGKFGKAFVGEIMKS*	Zasloff (1987)
	Magainin II	GIGKFLHSAKKFGKAFVGEIMNS*	Zasloff (1987)

GROUP NAME	PEPTIDE	SEQUENCE	REFERENCE*
	PGLa	GMASKAGAIAGKIAKVALKAL*	Kuchler et al. (1989)
	PGQ	GVLSNVIGYLKKLGTGALNAVLKG	Moore et al. (1989)
	XPF	GWASKIGQTLGKIAKVGLKELIQPK	Sures and Crippa (1984)
Mastoparans	Mastoparan	INLKALAALAKKIL*	Bernheimer and Rudy (1986)
Melittins	Melittin	GIGAVLKVLTTGLPALISWIKRKRQQ	Tosteson and Tosteson (1984)
Phormicins	Phormicin A	ATCDLLSGTGINHSACAAHCLLRGNRGGYCNGKGVCVCRN	Lambert et al. (1989)
	Phormicin B	ATCDLLSGTGINHSACAAHCLLRGNRGGYCNRKGVCVRN	Lambert et al. (1989)
Polyphemusins	Polyphemusin I	RRWCFRVCYRGFCYRKCR*	Miyata et al. (1989)
	Polyphemusin II	RRWCFRVCYKGFCYRKCR*	Miyata et al. (1989)
Protegrins	Protegrin I	RGGRLCYCRRRFCVCVGR	Kokryakov et al. (1993)
	Protegrin II	RGGRLCYCRRRFCICV	Kokryakov et al. (1993)
	Protegrin III	RGGGLCYCRRRFCVCVGR	Kokryakov et al. (1993)
Royalisins	Royalisin	VTCDLLSFKGQVNDSACAANCLSLGKAGGHCEKGVCICRKTSFKDLWDKYF	Fujiwara et al. (1990)
Sarcotoxins	Sarcotoxin 1A	GWLKKIGKKIERVGQHTRD	Okada and Natori

a9 cont

GROUP NAME	PEPTIDE	SEQUENCE	REFERENCE*
		ATIQGLGIAQQAANVAATA R*	(1985b)
	Sarcotoxin 1B	GWLKKIGKKIERVGQHTRD ATIQVIGVAQQAANVAAT AR*	Okada and Natori (1985b)
Seminal Plasmins	Seminalplasmin	SDEKASPDKHHRFSLSRYA KLANRLANPKLLETFLSKWI GDRGNRSV	Reddy and Bhargava (1979)
Tachyplesins	Tachyplesin I	KWCFRVCYRGICYRRCR*	Nakamura et al. (1988)
	Tachyplesin II	RWCFRVCYRGICYRKCR*	Muta et al. (1990)
Thionins	Thionin BTH6	KSCCKDTLARNCYNTCRFA GGSRPVCAGACRCKIISGP KCPSDYPK	Bohimann et al. (1988)
Toxins	Toxin 1	GGKPDLRPCIIPPCHYIPRPK PR	Schmidt et al. (1992)
	Toxin 2	VKDGYIVDDVNCTYFCGRN AYCNEECTKLKGESGYCQ WASPYGNACYCKLPDHVR TKGPGRCH	Bontems et al. (1991)

a9 cont'd

Please delete the paragraph on page 70, lines 7-9, and replace it with the following paragraph:

a10

The peptide was then purified by HPLC using a linear greadient of 0.1% TFA followed by enrichment with acetonitrile. The purified peptide was isolated and dried by lyophilization to yield cyclic CRGDC **(SEQ ID NO: 9)** in good yield.

Please delete the paragraph on page 71, line 18, and replace it with the following paragraph:

a11

This example is directed to the preparation of CRGDC <u>**(SEQ ID NO: 9)**</u> - branched PEG.

Please delete the paragraph on page 71, lines 19-23, and replace it with the following paragraph:

a12

The preparation of CRGDC <u>**(SEQ ID NO: 9)**</u> described in Example 1 is repeated followed by deprotection of the terminal Fmoc on the cysteine. After washing with DCM, MeOH, and DCM, the resin is then treated with three equivalents of DIC and one equivalent of phosphorylated branched PEG 2000 mixed anhydride from Example 2. The resin is reacted for four hours and coupling is tested for completion using the method of Kaiser.

Please delete the paragraph on page 72, lines 5-6, and replace it with the following paragraph:

a13

This example is directed to the preparation of CRGDC <u>**(SEQ ID NO: 9)**</u> - Branched PEG-amine.

Please delete the paragraph on page 72, lines 7-12, and replace it with the following paragraph:

a14

Branched PEG (4 Arm, 20K, Shearwater Corporation) is reacted with 4 equivalents of FMOC Glycine (American Peptide Company, Inc, CA), 1 equivalent of DIC and HOBT in DCM at room temperature for 4 hours. After deprotection, the product, HO-PEG-Glycine-NH_2, is purified by standard chromatographic techniques, and is then reacted with the peptide CRGDC <u>**(SEQ ID NO: 9)**</u> combining one equivalent of each reactant

a14 cont'd

using the methodology of Example 4.

Please delete the paragraph on page 72, lines 14-15, and replace it with the following paragraph:

a15

This example is directed to the preparation of CRGDC **(SEQ ID NO: 9)** - percarboxylated branched PEG.

Please delete the paragraph on page 72, lines 16-22, and replace it with the following paragraph:

a16

Branched PEG (4 Arm, 20K, Shearwater Corporation) is reacted with 4 equivalents of chloroacetic acid and 8 equivalents of sodium hydroxide for 90-120 minutes at room temperature. The reaction is quenched by addition of sodium dihydrigephosphate and adjusting the pH to 7.0, and the resulting product, percarboxylated branched PEG, is purified by dialysis. The percarboxylated branched PEG is then coupled with the CRGDC **(SEQ ID NO: 9)** peptide using the same coupling, cyclization, and isolation procedures as described in Examples 1 and 3.

Please delete the paragraph on page 75, line 25, through page 76, line 17, and replace it with the following paragraph:

a17

The peptide GGGRGDS **(SEQ ID NO: 121)** is produced by recombinant methods by intially synthesizing the DNA sequence GGC GGT GGG AGA GGA GAT AGT **(SEQ ID NO: 122)**. This is cloned into a Cre recombinase based expression vector. Cre recombinase facilitates site-specific recombination at *loxP* sites, and recognizes and binds to inverted repeats that flank the spacer region where recombination occurs. The enzyme uses a reactive tyrosine within its active site to cleave the DNA in the spacer region, creating a staggered cut with sticky ends. Cre then reattaches the 5' end of one *loxP* site to the 3' end of the other *loxP* at the site of the staggered cut, thus recombining the DNA

from two different vectors. Multiple reactions between the *loxP* site in pDNR and the two loxP sites in the acceptor vector occur simultaneously to transfer the gene and the chloramphenicol resistance gene into the acceptor vector. The plasmid is the Creator system available from Clontech (Palo Alto, CA). The acceptor vector in this case is an expression vector. The pTET-On (Clontech) vector expresses the exogenous gene in the presence of doxycycline. The vector is transferred into BL21-CodonPlus-RIL competent cells (Stratagene, La Jolla, CA). The genotype of these cells is strain[a] : *E. coli* B F– *ompT hsdS*(rB– mB–) *dcm*+ Tet^r *gal endA* Hte [*argU ileY leuW* Cam^r]. These cells are protease deficient and designed for high-level protein expression from T7 RNA polymerase-based expression systems. Derived from *E. coli* B, these strains naturally lack the Lon protease and are engineered to be deficient for the OmpT protease. The Lon and OmpT proteases found in other *E. coli* expression hosts may interfere with the isolation of intact recombinant proteins.

a 17 cont'd

Please delete the paragraph on page 76, lines 18-24, and replace it with the following paragraph:

a 18

The transformed cells are then grown in cell reactors to produce large quantities of GGGRGDS **(SEQ ID NO: 121)**. The protein is extracted using the one-step bacterial protein extraction reagent B-PER (Pierce, Rockford, IL). After a complete protein extraction, the extract is run through an Ultralink Biosupport Medium affinity column with a bound peptide that binds GGGRGDS **(SEQ ID NO: 121)** with high specificity (Pierce, Rockford, IL). After washing the column, the detergent concentration in the buffer is changed so that the GGGRGDS **(SEQ ID NO: 121)** is released and collected.

Please delete the paragraph on page 76, line 27, and replace it with the following paragraph:

a 19

The sequence for the basic fibroblast growth factor in humans is as follows: **(SEQ ID NO: 123)**

Please delete the paragraph on page 78, lines 3-16, and replace it with the following paragraph:

a20

The bFGF material is extracted from human cells in culture. The purified bFGF is then blunt end ligated to a linker peptide consisting of a repeat sequence of ACA (cysteine). The polymerase chain reaction method (PCR) is used to collect sufficient material. Two primers are designed with a melting temperature over 60_C, permitting the use of a higher annealing temperature in the PCR. The forward primer used is AGACATTAATGCGCTTCGATCG **(SEQ ID NO: 124)** and the reverse primer is GGCGGAGTAAAGGTAAAGCTGA **(SEQ ID NO: 125)**. The forward primer did not amplify the blunt end ligated section of ACA whereas the reverse primer did make that amplification. The PCR is carried out for 30 cycles with a 2 minute denaturation step at 95°C, a 30 second annealing step at 60_C and a 3 minute extension step at 72_C. The Taq Polymerase enzyme used in the PCR is most efficient at polymerizing DNA at 72_C. This amplification program provides more than a million fold amplification of the DNA with a terminal cysteine added at the 3' end. Sets of linkers and primers to add any of the amino acids at the 3' terminus of this sequence are also prepared.

Please delete the paragraph on page 82, lines 12-14, and replace it with the following paragraph:

a21

This example is directed to the preparation of N,N'-distearyldiaminobutryl-PEG3400-CRGDC **(SEQ ID NO: 9)** (cyclic) using standard solid-phase techniques with Fmoc protecting groups.

Please delete the paragraph on page 87, lines 12-20, and replace it with the following paragraph:

a22

This example is directed to the preparation of the following branched analog.

a22 cont'd

PEG-VVVVVK (SEQ ID NO: 126)
|
PEG-VVVVVK (SEQ ID NO: 126)
|
PEG-VVVVVK (SEQ ID NO: 126)
|
PEG-VVVVVK (SEQ ID NO: 126)

Please delete the paragraph on page 87, lines 25-26, and replace it with the following paragraph:

a23

B. Procedure

(1) Preparation of Fmoc-PEG$_{3400}$-VVVVV (SEQ ID NO: 127)

Please delete the paragraph on page 89, line 17, through page 90, line 5, and replace it with the following paragraph:

a24

The resin is washed using alternating washes of dichloromethane and methanol (2 x CH_2Cl_2, 2 x CH_3OH, 2 x CH_2Cl_2). To the washed resin is added 3 equivalents of Fmoc-Lys(Dde)-OH as a solid and 3 equivalents each of 1M HOBT/NMP and 1M DIC/NMP solutions. Sufficient NMP is added to cover the resin, and N_2 is bubbled up from the bottom of the reaction vessel to agitate, or by using a vortex mixer at 800 rpm. The mixture is stirred for approximately one hour and, if prepared by hand, a small amount of the resin is removed from the reaction vessel using a disposable pipette and placed on a paper filter. After washing with methanol and dichloromethane as described above, a portion of the washed resin is used to perform the Kaiser test. Excess of the washed resin is returned to the reaction vessel. If the test is negative (i.e., yellow solution), excess reagents are washed from the resin using alternating dichloromethane and methanol washes. If the test is positive (i.e., blue solution), the reaction is allowed to continue. If prepared on an automated synthesizer, the resin is washed after approximately 1 hour, without performing a Kaiser test. Any unreacted amine groups are capped using 5 drops

a[24] cont'd

each acetic anhydride and 5 drops triethylamine in DMF. This is allowed to react for 5 minutes, after which the solution is removed and the resin washed as previously described. These steps are repeated with Fmoc-Lys(Dde)-OH until completion of a four amino acid peptide sequence (i.e., Fmoc-$(K(Dde))_4$- Wang) (SEQ ID NO: 128).

Please delete the paragraph on page 90, lines 13-20, and replace it with the following paragraph:

a[25]

Fmoc-PEG-VVVVV-CO_2NHS (SEQ ID NO: 127) is coupled to Fmoc-KKKK-Wang (SEQ ID NO: 128) using 12 equivalents with 12 equivalents each of 1M HOBT/NMP and 1M DIC/NMP. The reaction is stirred under N_2, and the Kaiser test is used to monitor the reaction for completeness. Once the Kaiser test is negative, the resin is washed using dichloromethane and methanol, and the the Fmoc protecting group is removed from the amino acid-resin using 20% piperidine/NMP solution. After waiting 20 minutes, the solution is tested for free amine groups using Kaiser (ninhydrin) reagents. The resin is washed using alternating washes of dichloromethane and methanol.

Please delete the paragraph on page 91, lines 9-20, and replace it with the following paragraph:

a[26]

To the resin are added 3 equivalents of Fmoc-Val-OH and 3 equivalents each of 1M HOBT/NMP and 1M DIC/NMP solutions. Sufficient NMP is added to cover the resin, and N_2 is bubbled up from the bottom of the reaction vessel to agitate, or by using a vortex mixer at 800 rpm. The mixture is stirred for approximately one hour and, if prepared by hand, a small amount of the resin is removed from the reaction vessel using a disposable pipette and placed on a paper filter. After washing with methanol and dichloromethane as described above, a portion of the washed resin is used to perform the Kaiser test. Excess of the washed resin is returned to the reaction vessel. If the test is negative (i.e., yellow solution), excess reagents are washed from the resin using alternating dichloromethane and methanol washes. If the test is positive (i.e., blue solution), the reaction is allowed to

a26 cont'd

continue. These steps are repeated with Fmoc-Val-OH until completion of a six amino acid peptide sequence (i.e., Dde-K(Fmoc-VVVVV)-Wang) **(SEQ ID NO: 129)**.

Please delete the paragraph on page 92, lines 1-9, and replace it with the following paragraph:

a27

The resin is divided and a portion of which is set aside for later use. To cleave the Dde-K(methoxy-PEG-VVVVV) **(SEQ ID NO: 129)** from the resin, resin is added with stirring to a solution of 95% trifluoroacetic acid (TFA) in water (v/v). The mixture is allowed to stir for 20 minutes, and the mixture is filtered through a coarse fritted funnel. The resin is washed with TFA and water, and the filtrate and washings are combined and the pH adjusted to approx. pH 7 with aqueous 1N NaOH. The solution is placed in dialysis tubing (MW 1000 cutoff) for initial purification in 20 L. The volume of the resulting mixture is reduced, and the mixture is placed on a lyophilizer until a dry powder is obtained, which is subsequently purified using HPLC.

Please delete the paragraph on page 92, lines 10-15, and replace it with the following paragraph:

a28

The Dde protecting groups are removed from the retained Dde-K(methoxy-PEG-VVVVV) **(SEQ ID NO: 129)** using 2% hydzine in DMF. The reaction mixture is stirred at room temperature for 3 minutes, after which the resin is filtered and the hydrazine treatment is repeated two more times. The resin is washed with DMF and alternating washes of dichloromethane and methanol. The presence of free amines is checked using the Kaiser test, and the number of free amines is quantified using the Kaiser test.

Please delete the paragraph on page 92, lines 16-27, and replace it with the following paragraph:

a29

Dde-K(methoxy-PEG-VVVVV) **(SEQ ID NO: 129)** is coupled to the

a29 cont'd

deprotected K(methoxy-PEG-VVVVV) **(SEQ ID NO: 129)** using 3 equivalents with 3 equivalents each of 1M HOBT/NMP and 1M DIC/NMP. Sufficient NMP is added to cover the resin, and N_2 is bubbled up from the bottom of the reaction vessel to agitate, or by using a vortex mixer at 800 rpm. The mixture is stirred for approximately one hour and, if prepared by hand, a small amount of the resin is removed from the reaction vessel using a disposable pipette and placed on a paper filter. After washing with methanol and dichloromethane as described above, a portion of the washed resin is used to perform the Kaiser test. Excess of the washed resin is returned to the reaction vessel. If the test is negative (i.e., yellow solution), excess reagents are washed from the resin using alternating dichloromethane and methanol washes. If the test is positive (i.e., blue solution), the reaction is allowed to continue. These steps are repeated to form the final compound.

Please delete the paragraph on page 93, lines 5-6, and replace it with the following paragraph:

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a30

This example is directed to the preparation of CRGDS-PEG-LLLLLLLLL **(SEQ ID NO: 130)** using standard solid-phase techniques with Fmoc protecting groups.

Please delete the paragraph on page 93, line 16, through page 94, line 6, and replace it with the following paragraph:

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The resin is washed using alternating washes of dichloromethane and methanol (2 x CH_2Cl_2, 2 x CH_3OH, 2 x CH_2Cl_2). To the washed resin is added 3 equivalents of Fmoc-Lys(Dde)-OH as a solid and 3 equivalents each of 1M HOBT/NMP and 1M DIC/NMP solutions. Sufficient NMP is added to cover the resin, and N_2 is bubbled up from the bottom of the reaction vessel to agitate, or by using a vortex mixer at 800 rpm. The mixture is stirred for approximately one hour and, if prepared by hand, a small amount of the resin is removed from the reaction vessel using a disposable pipette and placed on a paper filter. After washing with methanol and dichloromethane as described above, a portion of the washed resin is used to perform the Kaiser test. Excess of the washed resin

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is returned to the reaction vessel. If the test is negative (i.e., yellow solution), excess reagents are washed from the resin using alternating dichloromethane and methanol washes. If the test is positive (i.e., blue solution), the reaction is allowed to continue. If prepared on an automated synthesizer, the resin is washed after approximately 1 hour, without performing a Kaiser test. Any unreacted amine groups are capped using 5 drops each acetic anhydride and 5 drops triethylamine in DMF. This is allowed to react for 5 minutes, after which the solution is removed and the resin washed as previously described. These steps are repeated with the next amino acid residue until completion of the decaleucine peptide sequence (i.e., Fmoc-$(L)_{10}$-OH) **(SEQ ID NO: 131)**.